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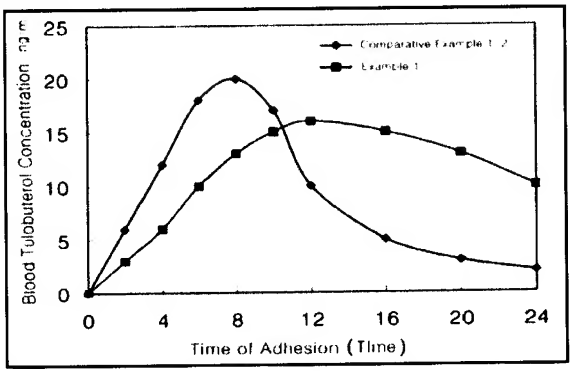
(54) Tulobuterol-containing Transdermal Delivery Preparation

Abstract

The present invention relates to a transdermal delivery preparation containing tulobuterol, a useful substance for treating dyspnoea of an asthma patient. More specifically, the present invention comprises a matrix layer containing tulobuterol, which is a treatment medicine for bronchial asthma, an acrylic adhesive, a skin permeation promoter and a dispersion enhancer, wherein the matrix layer has a thickness of 40 μm or thicker, and contains 1 weight % ~ 5 weight % of tulobuterol in a completely dissolved state.

Representative Drawing: Figure 1



Index: asthma, tulobuterol, transdermal delivery preparation

SPECIFICATION

<BRIEF EXPLANATION ON THE DRAWING>

FIG. 1 illustrates blood tulobuterol concentration with respect to the progress of time, which was experimented with rabbits each patching a transdermal delivery preparation, each obtained from EXAMPLE 1 (■) and COMPARATIVE EXAMPLE 1-2 (♦).

<DETAILED DESCRIPTION OF THE INVENTION>

[OBJECT OF THE INVENTION]

-TECHNIAL FIELD AND BACKGROUND ART-

The present invention relates to a delivery preparation containing tulobuterol, a useful substance for treating dyspnoea of an asthma patient.

Tulobuterol relaxes the bronchial smooth muscle by selectively affecting a beta 2 receptor of the sympathetic nerve. Accordingly, tulobuterol has been widely used for reducing or treating dyspnea of an asthma patient having tracheal stenosis. Tulobuterol is generally delivered inside the body by oral medication e.g. pills, anhydrous syrup, or inhalation e.g. aerosol. However, such methods have problems such as being difficult to apply to infants, having side effects of palpitation and tremor caused by rapid increase of tulobuterol concentration in the blood, and having a short durability.

In order to resolve these problems, there have been numerous efforts to develop a transdermal preparation which would help medicating tulobuterol through the surface of a patient's skin. There are several prior arts which relate to tulobuterol-containing transdermal delivery preparation e.g. Korean Patent Publication No. 1999-0064272, U.S. Patent No. 5,639,472 and U.S. Patent No. 5,312,627 which disclose a preparation containing tulobuterol which is dispersed into a solid or a micelle state by applying more tulobuterol to an adhesive layer, a plaster layer or a matrix layer than its solubility; Korean Patent Publication No. 1999-0062986 which discloses a preparation having a plaster layer containing more than 5 weight % of tulobuterol; and Korean Patent Publication No. 1991-0014113 and U.S. Patent No. 5,571,530 which disclose a transdermal delivery preparation having a specific kind of rubber adhesive.

However, if the adhesive layer, plaster layer or matrix layer contains more than 5 weight % of tulobuterol, or if the preparation contains tulobuterol dispersed into a solid or a micelle state, diurnal variations will occur to the stability and adherent property of tulobuterol as a shortcoming. Moreover, the transdermal delivery rate increases in proportion to the concentration of tulobuterol dissolved inside the matrix layer; however, if the size and quantity of the matrix layer is

identical, the matrix layer must be relatively thin in order to make a transdermal delivery preparation capable of containing highly-concentrated tulobuterol. Accordingly, a trandermal delivery preparation having a matrix layer which contains highly-concentrated tulobuterol would easily reach the highest concentration inside the blood at an early stage; however, 70% ~ 80% of the initial tulobuterol will penetrate through the skin within less than 12 hours, and the tulobuterol inside the matrix layer will dry up. After 12 hours, concentration of tulobuterol inside the blood will drop rapidly, and it would be difficult to keep a constant concentration throughout 24 hours. Moreover, the concentration of tulobuterol should be strictly kept below the side effect level since tulobuterol is a substance with a very narrow range of an effective concentration in the blood. However, preparations according to the above prior arts show rapid increase of concentration at an early stage after tulobuterol is released, and easily exceed the effective concentration in the blood, which could cause serious side effects. Such technical problem is not the kind that can be solved with the above-mentioned rubber adhesive.

-TECHNICAL PROBLEM TO BE SOLVED-

As shown above, there have been numerous attempts to develop a transdermal delivery preparation in order to solve the problems which oral or inhalant tulobuterol medications have; however, various obstacles remain unsettled. An object of the present invention is to overcome the shortcomings of these prior arts. To rephrase, the present invention relates a transdermal delivery preparation containing tulobuterol, a useful substance for treating bronchial asthma, and provides a once-a-day applicable transdermal delivery preparation of tulobuterol which releases tulobuterol in a constant manner and also maintains a certain level of tulobuterol concentration in the blood for 24 hours when applied to the surface of a patient's skin. The present invention also provides an excellent tulobuterol-containing transdermal delivery preparation which minimizes the diurnal variations to the stability and adherent property of tulobuterol which occur in accordance with the progress of time.

[CONSTITUTION AND PROCESS]

The present invention relates to a transdermal delivery preparation containing tulobuterol, a useful substance for treating dyspnoea of an asthma patient. The preparation further comprises a matrix layer including tulobuterol, which is a substance for treating bronchial asthma, an acrylic adhesive, a skin permeation promoter and a dispersion enhancer, wherein the matrix layer has a thickness of 40 μm or thicker, and contains 1 weight % ~ 5 weight % of tulobuterol in a completely dissolved state inside the layer.

The trandermal delivery preparation described in the present invention is preferable when the matrix contains 78 weight % ~ 97 weight % of an adhesive, 1 weight % ~ 20 weight % of a skin permeation promoter, and 1 weight % ~ 20 weight % of a dispersion enhancer, each with respect to the entire weight of the

matrix layer.

Tulobuterol, the substance used in the present invention, has a very narrow range of an effective concentration in the blood. Accordingly, its concentration should be strictly kept under the concentration where side effects start to occur. Also, in order to develop the preparation into a once-a-day type, the effective concentration of tulobuterol in the blood should be maintained in a constant manner for 24 hours. To achieve such object, the present invention provides a matrix layer thicker than 40 μm containing less than 5 weight % of tulobuterol in a completely dissolved state inside the matrix layer, so that the tulobuterol can be released in a constant manner for 24 hours.

Conducting a research for the present invention, it became clear that the transdermal rate is higher when applying a trandermal delivery preparation containing an acrylic adhesive, instead of a rubber adhesive disclosed in Korean Patent Publication No. 1991-0014113 and U.S. Patent No. 5,571,530 and U.S. Patent No. 5,312,627. Accordingly, the present invention has achieved its object by employing an acrylic adhesive as the adhesive ingredient. Further, an acrylic adhesive, wherein a monomer having hydroxyl group as a functional group is comprised as a main monomer shows especially high transdermal delivery rate compared to the rubber adhesive.

Accordingly, it would be preferable to arrange the adhesive used in the present invention to be an acrylic high-molecule polymer that maximizes the tulobuterol transdermal delivery, wherein a monomer having hydroxyl group as a functional group is comprised as a main monomer. Please refer to the examples of NSC 87-2287, NSC 87-2979, Soken 1570-1 and Soken 1570-2, etc.

A skin permeation promoter is used in the present invention to reduce the shortcomings of a long rag-time, the duration of time to reach an effective concentration in the blood once the preparation is applied to the skin. The skin permeation promoter according to the present invention is a high-quality fatty acid e.g. lauric acid, oleyl acid; high-quality fatty acid alcohol e.g. lauric alcohol, oleyl alcohol; glycerin fatty acid ester e.g. glycerol monolaurate; sorbitan fatty acid ester e.g. sorbitan monolaurate; polyethylene glycol sorbitan fatty acid ester e.g. polyethylene glycol sorbitan monostearate; terpenes e.g. menthol, menthol derivative and limonene; sulfoxides e.g. dimethylsulfoxide, dodecylsulfoxide; pyrrolidones e.g. N-methyl-2-pyrolidone; amides e.g. lauryldiethanolamide; N-hydroxy methyl-lactide, sorbitol, urea and their derivatives. Among these promoters, one selection or more than two selections can be used in the present invention.

It would be more preferable to select one or more ingredients from a group comprising lauric acid, oleyl acid, lauric alcohol, oleyl alcohol, glycerol monolaurate, sorbitan monolaurate, polyethylene glycol sorbitan monostearate, menthol derivative, limonene, dimethylsulfoxide, dodecylsulfoxide, N-methyl-2-pyrolidone, lauryldiethanolamide and ureal derivative as a skin permeation

promoter.

A dispersion enhancer is used in the present invention to enhance the dispersing of tulobuterol inside the thick matrix layer and to smooth the migration of the tulobuterol from the upper part of the matrix layer to the contact surface of the skin when the preparation is applied to a patient's skin, thereby releasing tulobuterol in a constant manner for a long duration of time. The dispersion enhancer according to the present invention is alcohols e.g. ethanol; high-quality fatty acid ether e.g. isopropyl myristate; polyethylene glycol fatty acid ether e.g. polyethylene glycol lauryl ether; polyethylene glycol fatty acid ester e.g. polyethylene laurate; propylene glycol fatty acid ether e.g. propylene glycol lauryl ether; propylene glycol fatty acid ester e.g. propylene glycol laurate; glycols e.g. propylene glycol, glycerin, polyethylene glycol, ethoxydiglycol; oils e.g. mineral oil. Among these enhancers, one selection or more than two selections can be used in the present invention.

It would be more preferable to select one or more ingredients from a group comprising isopropyl myristate, polyethylene glycol lauryl ether, polyethylene glycol lauryl ester, propylene glycol laurate, ethanol, propylene glycol, glycerin, polyethylene glycol and ethoxydiglycol as a dispersion enhancer.

Further, the supporting body of the transdermal delivery preparation according to the present invention should be something thin, flexible and non-responsive to skin so that it would not cause any allergic reactions. The release paper would support the product when the preparation is cut into an appropriate size, and when the product is actually applied to the skin, the release paper should not have any residue of the matrix layer when removed from the preparation.

In the present invention, a matrix layer having a thickness of 40 μm or thicker is used in order to make a once-a-day transdermal delivery preparation of tulobuterol and to keep the tulobuterol releasing in a constant manner for 24 hours. Further, less than 5% of tulobuterol is included in the adhesive matrix layer in a completely dissolved state so that tulobuterol would be released in a constant manner for 24 hours, and accordingly minimize diurnal variations to the stability and adherent property of tulobuterol which occur in accordance with the progress of time. A trandermal delivery preparation with a matrix layer thicker than 40 μm and containing less than 5 weight % of tulobuterol provides longer duration of tulobuterol effect when the preparation is applied to the skin; however, its transdermal delivery rate is relatively lower than other highly-concentrated preparations and further, its rag-time, which refers to the duration of time to reach an effective concentration in the blood, is longer. Thus, in order to improve the lower delivery rate, the present invention uses an acrylic adhesive wherein a monomer having hydroxyl group as a functional group is comprised as a main monomer. In order to reduce the rag-time, the present invention uses a skin permeation promoter to disturb the delivery barrier of the skin and promote the penetration speed into the skin. Further, the present invention co-employs an additive which enhances tulobuterol's dispersion inside

the matrix layer and promotes tulobuterol to migrate from the upper part of the matrix layer to the contact surface of the skin when the preparation is applied, thereby releasing tulobuterol in a constant manner for a long duration time.

Set below are Examples to specify the subject invention; however, theses Examples are only examples of the present invention and thus, the present invention shall not be limited by the following Examples.

Example 1

Tulobuterol	4 weight %
Acrylic Adhesive (NSC 87-2287)	88 weight % (dry weight)
Glycerol Monolaurate	4 weight %
Isopropyl Myristate	4 weight %

Manufacturing Process

(1) Tulobuterol, glycerol monolaurate, isopropyl myristate were put into the acrylic adhesive and mixed, and then were melted completely.
(2) On the release paper, it was coated with a thickness-after drying of 50 μm.
(3) It was dried at 60°C for 30 minutes in an oven.
(4) A patch was made by laminating a polyethylene film.

Comparative Example 1-1

Tulobuterol	4 weight %
Rubber Adhesive (MA-24)	92 weight % (dry weight)
Glycerol Monolaurate	4 weight %

Manufacturing Process

(1) Tulobuterol and glycerol monolaurate were put into the rubber adhesive and mixed, and then were melted completely.
(2) On the release paper, it was coated with a thickness-after drying of 50 μm.
(3) It was dried at 60°C for 30 minutes in an oven.
(4) A patch was made by laminating a polyethylene film.

Comparative Example 1-2

Tulobuterol	10 weight %
Acrylic Adhesive (NSC 87-2287)	86 weight % (dry weight)
Glycerol Monolaurate	4 weight %

Manufacturing Process

(1) Tulobuterol and glycerol monolaurate were put into the acrylic adhesive and mixed, and then were melted completely.

(2) On the release paper, it was coated with a thickness-after drying of 20 μm.
(3) It was dried at 60°C for 30 minutes in an oven.
(4) A patch was made by laminating a polyethylene film.

Example 2

Tulobuterol	4 weight %
Acrylic Adhesive (NSC 87-2979)	84 weight % (dry weight)
Lauryldiethanolamide	6 weight %
Ethoxydiglycol	6 weight %

Manufacturing Process

(1) Tulobuterol, lauryldiethanolamide and ethoxydiglycol were put into the acrylic adhesive and mixed, and then were melted completely.
(2) On the release paper, it was coated with a thickness-after drying of 50 μm.
(3) It was dried at 60°C for 30 minutes in an oven.
(4) A patch was made by laminating a polyethylene film.

Comparative Example 2-1

Tulobuterol	10 weight %
Rubber Adhesive (NSC 87-6172)	84 weight % (dry weight)
Lauryldiethanolamide	6 weight %

Manufacturing Process

(1) Tulobuterol and lauryldiethanolamide were put into the rubber adhesive and mixed, and then were melted completely.
(2) On the release paper, it was coated with a thickness-after drying of 20 μm.
(3) It was dried at 60°C for 30 minutes in an oven.
(4) A patch was made by laminating a polyethylene film.

Comparative Example 2-2

Tulobuterol	10 weight %
Acrylic Adhesive (NSC 87-2979)	84 weight % (dry weight)
Lauryldiethanolamide	6 weight %

Manufacturing Process

(1) Tulobuterol and lauryldiethanolamide were put into the acrylic adhesive and mixed, and then were melted completely.
(2) On the release paper, it was coated with a thickness-after drying of 20 μm.
(3) It was dried at 60°C for 30 minutes in an oven.
(4) A patch was made by laminating a polyethylene film.

Example 3

Tulobuterol	3 weight %
Acrylic Adhesive (Soken 1570-1)	87 weight % (dry weight)
Sorbitan Monolaurate	5 weight %
Polyethylene Glycol Lauryl Ether	5 weight %

Manufacturing Process

(1) Tulobuterol, sorbitan monolauratem and polyethylene glycol lauryl ether were put into the acrylic adhesive and mixed, and then were melted completely.
(2) On the release paper, it was coated with a thickness-after drying of 67 μm.
(3) It was dried at 60°C for 30 minutes in an oven.
(4) A patch was made by laminating a polyethylene film.

Example 4

Tulobuterol	3 weight %
Acrylic Adhesive (Soken 1570-2)	87 weight % (dry weight)
Sorbitan Monooleate	5 weight %
Propylene Glycol Laurate	5 weight %

Manufacturing Process

(1) Tulobuterol, sorbitan monooleate and propylene glycol laurate were put into the acrylic adhesive and mixed, and then were melted completely.
(2) On the release paper, it was coated with a thickness-after drying of 67 μm.
(3) It was dried at 60°C for 30 minutes in an oven.
(4) A patch was made by laminating a polyethylene film.

Example 5

Tulobuterol	4 weight %
Acrylic Adhesive (NSC 87-2287)	43 weight % (dry weight)
Acrylic Adhesive (NSC 87-2979)	43 weight % (dry weight)
Glycerol Monolaurate	6 weight %
Isopropyl Myristate	4 weight %

Manufacturing Process

(1) Tulobuterol, glycerol monolaurate and isopropyl myristate were put into two types of acrylic adhesives and mixed, and then were melted completely.
(2) On the release paper, it was coated with a thickness-after drying of 50 μm.
(3) It was dried at 60°C for 30 minutes in an oven.
(4) A patch was made by laminating a polyethylene film.

Example 6

Tulobuterol	4 weight %
Acrylic Adhesive (NSC 87-2287)	43 weight % (dry weight)
Acrylic Adhesive (NSC 87-2979)	43 weight % (dry weight)
Sorbitan Monolaurate	5 weight %
Propylene Glycol Laurate	5 weight %

Manufacturing Process

(1) Tulobuterol, sorbitan monolaurate and propylene glycol laurate were put into two types of acrylic adhesives and mixed, and then were melted completely.
(2) On the release paper, it was coated with a thickness-after drying of 50 μm.
(3) It was dried at 60°C for 30 minutes in an oven.
(4) A patch was made by laminating a polyethylene film.

Experimental Example 1: Transdermal delivery

The hair on the stomach area of a male guinea pig which weighs approximately 350g was cut with an electric hair clipper and then completely shaved with a shaver. The full skin of a certain area of its stomach was abstracted and was frozen below -20°C for reservation. The full skins were melted each time for experiments.

Once the skin has melted, they were cut by 2 × 2 cm^2, and the patches from Examples and Comparative Examples were cut by 1.5 × 1.5 cm^2 and then patched to the skin cell layer of each of the skin.

The skins were set so that the part where a patch is applied to the franz-type dispersion cell faces upward. A phosphoric acid buffer solution of pH 7.4 was put into the space at the lower part and the temperature of the diffuser was kept at 37 °C. The receptor solution (buffer solution) was mixed at a constant speed of 600 rpm. After a pre-determined duration of time, an appropriate amount of the receptor solution was abstracted and replaced the taken amount with a new receptor solution. The concentration of the abstracted sample was measured by using high-performance liquid chromatography (HPLC) which results are indicated in Table 1 below.

[Table 1]

Amount of tulebuterol delivered through skin experimented by applying a thransdermal delivery preparation to the skin of a guinea pig

Patch No.	Average Skin Delivery Rate (μg/cm^2/hr)				
	0~3hrs.	3~6hrs.	6~9hrs.	9~12hrs.	12~24hrs
Example1	5.7	10.2	12.2	10.7	7.2
C.Example 1-1	1.7	3.3	4.7	3.2	2.4
C.Example 1-2	6.5	17.3	14.7	7.2	3.4
Example 2	4.8	9.6	11.8	11.3	7.5

C.Example 2-1	2.9	4.9	6.6	5.5	3.2
C. Example 2-2	5.9	15.9	13.6	6.5	3.2
Example 3	3.7	9.4	10.6	9.1	6.9
Example 4	4.0	9.6	10.8	9.7	6.5
Example 5	5.3	10.9	12.0	10.9	7.4
Example 6	5.4	10.7	11.5	10.2	7.7

Example 1 and Comparative Example 1-1 was experimented with identical amount of tulebuterol (4%); however, as shown in Table 1 above, the result differs in accordance with the type of adhesive used in the matrix layer. Skin delivery rate of Example 1 using an acrylic adhesive was remarkably higher than that of Comparative Example 1-1 using a rubber adhesive. Moreover, a different type of rubber adhesive from Comparative Example 1-1 was used in Comparative 2-1 and even the amount of tulobuterol was increased to 10%; however, the skin delivery rate was shown remarkably higher in Examples 1 and 2 using an acrylic adhesive though the amount of tulobuterol was only 4%. Further, in comparison to Examples 1 and 2, Comparative Examples 1-2 and 2-2 was manufactured without including any dispersion enhancers. Comparative Examples 1-2 and 2-2 presented remarkable skin delivery rate until the 9^{th} hour; however, the rate rapidly started to drop since the 12^{th} hour. Also, Examples 3, 4, 5 and 6 each has different types of acrylic adhesives and they all presented excellent skin delivery rate compared to other Comparative Examples using rubber adhesives.

Experimental Example 2: Change of blood tulobuterol concentration in a rabbit

The change of blood tulobuterol concentration was experimented on a rabbit by shaving its back hair in advance and patching the transdermal delivery preparation obtained from Example 1 and Comparative Example 1-2.

The result of the above experiment is illustrated in FIG. 1.

<Blood tulobuterol concentration experiment process>

Sample Size:	10 cm^2
Applied Area:	Shaved back of a rabbit
Duration:	24 hours
Method for measuring concentration:	Gas chromatography

Example 1 and Comparative Example1-2 used identical type of acrylic adhesive. However, as shown in FIG. 1, Comparative Example 1-2, which had high concentration of tulobuterol in the matrix layer and did not have any dispersion enhancers, presented high numbers until the 8^{th} hour in comparison to Example 1, which had low concentration of tulobuterol in the matrix layer and had a dispersion enhancer. However, Example 1 shows far more excellent maintenance of blood tulobuterol concentration for the whole 24 hours

compared to Comparative Example 1-2.

Experimental Example 3: Stability of tulobuterol inside the patch

The manufactured patch was put into an aluminum pack and filled with nitrogen gas, and then sealed. The pack was reserved in an oven with the condition of 40°C and relative humidity of 75%. After a specific amount of time has passed, the pack was opened and tulobuterol was abstracted and its residue was measured by using high-performance liquid chromatography (HPLC) which results are indicated in Table 2 below.

[Table 2]
Stability of tulobuterol inside the patch

Patch No.	Residue Amount (%)			
	1 month	2 months	3 months	6 months
Example1	99.3	98.5	97.2	95.6
C.Example 1-1	99.3	98.7	97.6	96.0
C.Example 1-2	96.3	92.7	90.6	85.4
Example 2	98.7	97.4	96.0	94.8
C.Example 2-1	98.1	94.2	91.7	85.3
C. Example 2-2	97.1	95.2	92.7	88.3
Example 3	99.1	98.3	97.6	96.4
Example 4	99.2	98.4	97.5	96.3
Example 5	98.9	98.1	96.6	95.2
Example 6	98.8	97.9	96.4	94.1

Example 1 and Comparative Example 1-1 both used identical amount of tulobuterol (4%) but different types of adhesive; however, as shown in Table 2 above, there is no significant difference in the stability of tulobuterol according to whether an acrylic adhesive or a rubber adhesive was used. However, comparing Example 1 and Comparative Example 1-2, and comparing Example 2 and Comparative Examples 2-1, 2-2 which had different amount of tulobuterol, the stability of tulobuterol was significantly lower in Comparative Examples 1-2, 2-1, 2-2 which had higher concentration of tulobuterol in the matrix layer than Examples 1 and 2. Further, Examples 3, 4, 5 and 6 each had different types of adhesives and low concentration of tulobuterol inside the matrix layer; however, they all presented excellent stability of tulobuterol compared to other Comparative Examples.

Experimental Example 4: Adhesive strength of the patch

The manufactured patch was put into an aluminum pack and filled with nitrogen gas, and then sealed. The pack was reserved in an oven with the conditions of 40°C and relative humidity of 75%. After a specific amount of time has passed, the pack was opened and tested the stability of its adhesive strength based on the progress of time. Each patch was cut into 15 × 2.5 cm^2 and affixed it to a

stainless steel plate, and then rolled a roller (500g) over the patch twice in a to-and-fro motion in order to adhere the patch more intimately to the plate. After leaving it for 30 minutes, the patch's adhesive strength was tested with an adhesive strength tester (Texture Analyzer Model XT2i, Stable Micro Systems). The adhesive strength was tested by peeling the patch in a speed of 300mm/min, in a direction that forms 180°, under the conditions of 25°C and relative humidity of 65%. The result of the experiment is indicated in Table 3.

[Table 3]
Stability of the patch's adhesive strength
in accordance with the progress of time

Patch No.	Adhesive Strength (g/inch)	
	Initial Stage	40°C, 3 months later
Example1	565	551
C.Example 1-1	383	312
C.Example 1-2	483	312
Example 2	418	420
C.Example 2-1	412	315
C. Example 2-2	512	355
Example 3	530	498
Example 4	567	534
Example 5	453	448
Example 6	427	417

Example 1 and Comparative Example 1-1 comprises identical amount of tulobuterol (4%); however, as shown in Table 3 above, Example 1 wherein an acrylic adhesive is used had far more excellent adhesive strength compared to Comparative Example 1-1 wherein a rubber adhesive is used. Comparing Example 1 and Comparative Example 1-2, and comparing Example 2 and Comparative Examples 2-1, 2-2 which had different amount of tulobuterol, adhesive strength in accordance with the progress of time was significantly lower in Comparative Examples 1-2, 2-1, 2-2 which had higher concentration of tulobuterol in the matrix layer than Examples 1 and 2. Further, Examples 3, 4, 5 and 6 each had different compositions of acrylic adhesives and low concentration of tulobuterol inside the matrix layer; however, they all presented excellent adhesive strength in accordance with the progress of time compared to other Comparative Examples.

[EFFECTS OF THE INVENTION]

The transdermal delivery preparation of the present invention maintains a certain level of tulobuterol concentration inside the blood by releasing tulobuterol in a constant manner once the patch is applied to the skin. The patch can be applied once a day and be effective for 24 hours and further prevents an asthma patient's dawn seizures. Also, the transdermal delivery preparation of the present invention minimizes diurnal variations to the stability and adherent

property of the tulobuterol which occur in accordance with the progress of time, and therefore provides excellent transdermal delivery preparation of tulobuterol.

(57) CLAIMS

Claim 1

A transdermal delivery preparation comprising a matrix layer containing tulobuterol, an acrylic adhesive, a skin permeation promoter and a dispersion enhancer, wherein the matrix layer has a thickness of 40 μm or thicker and contains 1 weight% ~ 5 weight% of tulobuterol in a completely dissolved state inside the layer.

Claim 2

A transdermal delivery preparation according to Claim 1, wherein an adhesive has 78 weight % ~ 97 weight % with respect to the entire weight of the matrix layer, a skin permeation promoter has 1 weight % ~ 20 weight % with respect to the entire weight of the matrix layer, and a dispersion enhancer has 1 weight % ~ 20 weight % with respect to the entire weight of the matrix layer.

Claim 3

A transdermal delivery preparation according to Claim 1, characterized in that said acrylic adhesive is an acrylic high-molecule polymer, wherein a monomer having hydroxyl group as a functional group is comprised as a main monomer.

Claim 4

A transdermal delivery preparation according to Claim 1, wherein the skin permeation promoter is one or more ingredients selected from a group comprising high-quality fatty acid; high-quality fatty acid alcohol; glycerin fatty acid ester; sorbitan fatty acid ester; polyethylene glycol sorbitan fatty acid ester; terpenes; sulfoxides; pyrrolidones; amides; N-hydroxy methyl-lactide, sorbitol, urea and their derivatives.

Claim 5

A transdermal delivery preparation according to Claim 4, wherein the skin permeation promoter is one or more ingredients selected from a group comprising lauric acid, oleyl acid, lauric alcohol, oleyl alcohol, glycerol monolaurate, sorbitan monolaurate, polyethylene glycol sorbitan monostearate, menthol derivative, limonene, dimethylsulfoxide, dodecylsulfoxide, N-methyl-2-pyrolidone, lauryldiethanolamide and ureal derivative.

Claim 6

A transdermal delivery preparation according to Claim 1, wherein the dispersion enhancer is one or more ingredients selected from a group comprising alcohols; high-quality fatty acid ester; polyethylene glycol fatty acid ether; polyethylene glycol fatty acid ester; propylene glycol fatty acid ether; propylene glycol fatty acid ester; glycols; and oils.

Claim 7

A transdermal delivery preparation according to Claim 6, wherein the dispersion enhancer is one or more ingredients selected from a group comprising isopropyl myristate, polyethylene glycol lauryl ether, polyethylene glycol lauryl ester, propylene glycol laurate, ethanol, propylene glycol, glycerin, polyethylene glycol and ethoxydiglycol.

[DRAWING]

FIG. 1